

## INVOLVEMENT OF THE EYE IN PROTEIN MALNUTRITION \*

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### SYNOPSIS

An extensive review of the literature on protein malnutrition, with special reference to the frequency of involvement of the eyes, has been made by the author. Consideration of accounts from all parts of the world and in many different languages, including early as well as more recent descriptions of the syndrome, indicates that this important complication has not received sufficient attention hitherto. The evidence available suggests that it is nearly always an accompanying deficiency of vitamin A that is responsible. Less commonly reported—and producing less severe effects—is deficiency of the B-complex vitamins, and there is no clear evidence to date that protein deficiency itself damages the eyes in these cases.

The ways in which protein lack might interfere with various aspects of vitamin-A metabolism are discussed, but it is pointed out that their actual significance in human disease is not yet known. A low dietary intake of vitamin A is regarded by the author as being the prime factor in the causation of eye complications, and attention is drawn to the necessity to correct this as part of any prophylactic or therapeutic programme aimed primarily at combating protein malnutrition.

The syndrome known by such various names as kwashiorkor, nutritional oedema syndrome, síndrome pluricarenal, and many others (Trowell, Davies & Dean, 1954), and characterized chiefly by a dietary deficiency of protein, has been reported as occurring amongst most of the malnourished communities of the world. The clinical picture varies in certain details from place to place, and whilst some of these differences remain unexplained, others appear to be adequately accounted for by the presence or absence of accompanying vitamin deficiencies.

It is generally held that where involvement of the eyes occurs deficiency of vitamin A or of vitamins of the B complex is responsible. The conclusions resulting from this present review of the literature only serve to confirm this opinion. So far there appears to be no real evidence to support the view

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sometimes put forward that protein deficiency alone may result in eye lesions in man. It is conceivable that protein malnutrition may adversely affect various aspects of the metabolism of vitamin A and this point will be taken up later, but where true xerophthalmia accompanies deficiency of protein a very low intake of the vitamin or provitamin is usually found as an adequate explanation.

Whilst the eyes, especially in their anterior segment, are readily accessible to examination by the clinician, their condition in protein malnutrition has not been consistently reported, and it will be necessary to distinguish between those areas of the world from which eye signs have been reported as not occurring, and those from which reports have failed to mention the eye. The former type of report will be quoted in this review, and it may be safely assumed that other reports of protein malnutrition, not mentioned here, have failed to comment on the state of the eyes.

Despite the considerable neglect which the eye has suffered in this respect, the large number of reports which will shortly be mentioned which describe its involvement in cases of protein malnutrition will fully justify the making of such a review generally known. Many general accounts of the condition have been written by people who have worked in areas where eye lesions are uncommon, and in their reviewing of the literature from parts with which they were not personally familiar, they have failed to consult the writings of workers who have approached the subject from an ophthalmological point of view. Even such an excellent monograph as that of Trowell, Davies & Dean mentions reports of involvement of the eye from only three countries—Indonesia, India, and Mexico. That this treatment is less than justice will now be shown.

## Review of Literature

### *Asia*

It is appropriate to begin with that part of the world from which most accounts of a high incidence of xerophthalmia and keratomalacia have come in the past. The blinding results of vitamin-A deficiency were recognized and described before the equally serious results of protein deficiency, although both these conditions have their maximum effect in the pre-school age-group, and frequently attack the same child. Thus, long before Oomen (1953, 1955) drew attention to the very high prevalence (about 70%) of xerophthalmia in children with kwashiorkor in Macassar and Djakarta in Indonesia, De Haas, Posthuma & Meulemans (1940) found a similarly high prevalence of general dystrophy in their cases of xerophthalmia in the Central Hospital, Batavia (now Djakarta). From Kalimantan (formerly Netherlands Borneo) Hoogenkamp (1956) has described 91 cases of avitaminosis A, 57% of which had enlarged livers, and of 14 biopsies, 11 showed steatosis. Yap Kie Tiong (1956), an ophthalmologist working in Jogjakarta,

who treats hundreds of cases of xerophthalmia and keratomalacia every year, is of the opinion that protein deficiency is responsible for the total colliquative necrosis of the cornea in the most advanced stage.

Early accounts of keratomalacia in China frequently mention systemic signs suggestive of an accompanying protein deficiency. The 10 cases of keratomalacia treated by Hsu (1927) had general dystrophy, and Keefer & Yang (1929) found that of 11 infants fed exclusively on milk for many months and having anaemia and undernutrition, 3 also had keratomalacia. Weech (1930) in Peiping noted oedema in 5 of his 13 cases of keratomalacia in children under the age of 3½ years, and called attention to the marked undernutrition of the entire group, expressing the opinion that the oedema was not an expression of deficiency of vitamin A but of an associated nutritional disorder. Eleven of the 203 cases of xerophthalmia of Sweet & K'Ang (1935) were also suffering from nutritional oedema and in all cases in which the serum albumin was determined it was found to be low. More recently Chen (1942) described the frequent presence of keratomalacia in children in Shanghai suffering from nutritional oedema and regarded this as the most noticeable evidence of vitamin deficiency in these children. However, according to Platt (personal communication), who has recently toured the country and was able to compare present conditions with those prevailing before the Second World War, vitamin-A deficiency has almost disappeared, but protein malnutrition occurs, although it is frequently not recognized.

From India, one of the best known accounts of keratomalacia (Wright, 1931) mentions the frequent association with liver disease, and although the writer, an ophthalmologist, terms the condition biliary cirrhosis, it may well have been part of protein malnutrition. Kirwan, Sen & Bose (1943), in their description of keratomalacia in Bengali children, mention that they were emaciated, with distended abdomen, dry, brittle and scanty hair, and loose, dry and dark skin, and that diarrhoea was often present. The systemic effects of vitamin-A deficiency in man are not clearly defined, and indeed are likely to be accompanied by those of caloric and protein lack. The situation in Bengal would seem to be rather similar to that in the neighbouring province of Orissa, where the writer failed to find eye signs in cases of kwashiorkor, and children with keratomalacia were also marasmic (McLaren, 1956). Recent accounts of a high incidence of eye signs attributable to vitamin-A deficiency in children with protein malnutrition come from Madras (Achar, 1950; Achar & Benjamin, 1953), Coonoor (Gopalan, 1955) and Poona (Khalap, 1956).

From Ceylon, Jayasekera, De Mel & Cullumbine (1951) mention that of their 40 cases of "fatty liver disease", 19 had xerosis, but they give no further details.

A very interesting early description of protein malnutrition, not previously recognized to the writer's knowledge, comes from Malaya (Martin,

1930). In this paper, entitled "Observations on cases of keratomalacia" and illustrated with clinical photographs, mention is made that besides the eye lesions, these children had "harsh skin, emaciation, oedema, and a look of misery". General improvement took place on a good hospital diet and liver-extract treatment. Recently, Said (1955) in Negri Sembilan found that keratomalacia was the reason for six children, who were also suffering from protein malnutrition, being brought to hospital.

A monograph on malnutrition and nutrition activities in Japan, prepared for the fourth meeting of the Nutrition Committee for South and East Asia, sponsored by FAO and WHO and held at Tokyo in September-October 1956, states that infants and children with protein malnutrition frequently develop a vitamin deficiency, of which vitamin-A deficiency is the most common. This sometimes leads to loss of sight. Also from Japan comes the description (Irinoda & Sato, 1954) of a nutritional disorder known locally as "shibi" and "gattchaki", and attributed to deficiency of riboflavine. The disease affects chiefly the skin, mucous membranes and the eye. The following ocular lesions are said to be part of the syndrome: angular blepharo-conjunctivitis; hyperaemia, vascularization and pigmentation at the corneal limbus; superficial diffuse keratitis; temporal pallor, redness, and opacity of the optic nerve.

In the Philippines, the combination of keratomalacia with protein malnutrition has been reported from Manila (Stransky, 1950; Stransky, Daus-Lawas & Lawas, 1951) and Jelliffe (1955) found that vitamin-A deficiency was common and frequently associated with diarrhoea, ascariasis and kwashiorkor.

Finally, for the sake of convenience, the only report from Australasia is included here. Manson-Bahr (1951), in an account of three fatal cases of kwashiorkor in Fijian children, described keratomalacia in one which he thought was probably caused by an associated vitamin-A deficiency. The combination appears to be uncommon here, for in a series of a further 16 cases of kwashiorkor, the same worker makes no mention of involvement of the eye (1952).

### *The Middle East and North Africa*

These areas are best considered together. The Middle East provides very few descriptions of protein malnutrition, although vitamin-A deficiency is common, and the writer has found no account of the two conditions being associated. That they may sometimes coexist is suggested by two accounts from North Africa.

In Egypt, Hanafy (1948) has described protein malnutrition in Alexandria, under the title "The subacute subnutritional syndrome in infants". Of his 197 cases, 90% were 1-3 years old. Eye changes were frequent, and attributed by him to deficiency of vitamin A and riboflavine. They consisted

of conjunctival injection, with red, dry, occasionally (13 cases) fleshy masses over the conjunctiva; the cornea was sometimes dull and vascularized. Ulcerations and staphylomata were not infrequent.

From Casablanca, Delon (1951) reported 10 cases of kwashiorkor, two of which had xerophthalmia. Most of the children had photophobia.

### *Africa South of the Sahara*

In West Africa the widespread consumption of the oil of the red palm (*Eloeis guineensis*) makes severe vitamin-A deficiency uncommon, but even so, Thompson (1956b) has recently reported its prevalence in Northern Nigeria, and has also described keratomalacia accompanying a fatal case of kwashiorkor in the same area (1956a).

The classical descriptions of Williams (1933, 1935) from Ghana make special mention of the fact that whilst Bitot's spots, night blindness, and xerophthalmia occurred in other members of the same population, they had not been observed in kwashiorkor. It would be interesting to know whether this statement still holds true there.

In French West Africa, the anterior segment of the eye is fairly frequently affected in common with other mucous membranes and the lesions described as "granular conjunctivitis and keratoconjunctivitis, with haemorrhagic subconjunctival suffusions" (Bergounion & Raoult, 1952) and "subacute conjunctivitis" (Grall, 1950) are suggestive most of vitamin-B-complex deficiency. However, Dupon (personal communication) says that some protein malnutrition cases in Dakar also have xerophthalmia. An early description (Lieurade, 1932) of eye involvement in protein malnutrition comes from French Cameroon, where mention is made of marked palpebral pigmentation nearly always accompanied by an oculo-nasal discharge.

In East Africa vitamin-A deficiency appears to be quite common, but has rarely been reported in association with protein malnutrition. One of Trowell's early cases (Trowell, 1937) had keratomalacia, and recently plasma vitamin-A and carotenoid values in his cases of kwashiorkor have proved to be low, although clinical eye signs were absent (Trowell, Moore & Sharman, 1954). The writer was recently shown some kwashiorkor cases in Mombasa, Kenya, one of whom had advanced xerosis conjunctivae and corneae and another the "spontaneous clean prolapse of iris" which also occurs commonly in the South African Bantu child, as will be seen later. Davies has raised the important question of whether the lacrimal glands are involved in protein deficiency, and if so, whether changes there may result in secondary lesions of the anterior segment of the eye (see Trowell, Davies & Dean, 1954). He has described atrophic changes in the lacrimal glands in kwashiorkor, similar to those found in the pancreas and salivary glands.

In Central Africa protein malnutrition is common, but the eye is not usually affected. Van Daele (1938) makes special mention of the fact that there were no eye signs in any of his cases in the Congo. However, in the highlands of Ruanda Urundi, the red palm does not grow and vitamin-A deficiency is very common (Roels, Debeir & Trout, 1957). Roels (personal communication) states that some of the children with kwashiorkor also have xerophthalmia.

Coming finally to South Africa, one finds that whilst protein malnutrition is rife amongst the Bantu population, xerophthalmia does not appear to accompany it frequently. When the eyes are affected the symptoms seem more suggestive of a vitamin-B-complex deficiency (Kark, 1943; Klenerman, 1950). But under vitamin-A deficiency Klenerman also mentions that ocular disturbances which were destructive to the sight of the patient were found in several instances. Of outstanding interest is the condition described as "malnutritional keratitis" by Blumenthal (1950, 1954) in young Bantu children in East London. There seems to be little doubt that these children were suffering from protein malnutrition and that the corneal lesions were quite different from keratomalacia. This is certainly true of the "spontaneous clean prolapse of iris", of which mention has already been made. However, some of the other types of lesion which Blumenthal includes are of more doubtful significance. The precise etiology of this important and possibly widespread condition is still unknown, and further reports and results of treatment may be eagerly awaited.

### *Central America*

Autret & Behar (1954), in their account of protein malnutrition in Central America, state that the workers met with often mentioned keratomalacia, opacity and ulceration of the cornea. This indication of the prevalence of the association of these conditions in this area is borne out by a number of individual reports. According to Waterlow (1948), keratomalacia was a prominent feature of the syndrome described by Gil (1934) in Mexico. In Mexico City, Pagola (1948) found that in 500 cases of protein malnutrition, 90% had signs of vitamin-A deficiency as judged by the diminished humidity of the conjunctiva under the biomicroscope. Of these, 78% had early xerosis, 7% had xerophthalmia with corneal ulcer and 12% had keratitis, and Bitot's spots were seen in 1.3%. Blood titres of vitamin A and carotene were as low as 10-20 units per 100 grams. He attributed keratitis in 12% and engorgement of the circumcorneal veins in 62% to riboflavine deficiency. The cases of Turnbull (1951), again in Mexico, also seem to have had ocular features resulting from deficiency of vitamins of the B complex.

In Honduras, Vidal (1938) described conjunctivitis and xerosis as occasional features of protein malnutrition.

From Guatemala comes the report of consistently low carotene and vitamin-A serum levels (Scrimshaw et al., 1955a, 1955b). However, in the experience of Scrimshaw and his co-workers these biochemical changes do not appear to have been accompanied by clinical eye lesions.

Castellanos (1935), cited by Trowell (1940), found that in Cuba xerophthalmia was frequently associated with protein malnutrition, and he later (1937) stated that 10 of his cases had xerophthalmia.

In the British West Indies, however, vitamin-A deficiency appears to be rare (Jelliffe, 1955), and no report of eye signs accompanying the general malnutrition which is so common there is known.

### *South America*

A recent review (Waterlow & Vergara, 1956) of protein malnutrition in Brazil does not mention the eye, but Carvalho (1946, 1947) in Rio de Janeiro found hemeralopia and xerophthalmia in 16 of his 58 cases, and Pernetta & De Martino (1945), in the same city, state that 2 of their 7 cases had xerosis conjunctivae.

In Caracas, Venezuela, Oropeza (1946) found a very high rate (50%) of conjunctival hyperaemia and excess lacrimal secretion among his 114 cases. Xerophthalmia is also mentioned as occurring.

Meneghello and his associates (1949, 1950) in Santiago, Chile, state that the avitaminoses were subclinical, but that vitamin-A deficiency was detected by demonstration of keratinization of the cornea. Quoting Maffioletti (1945), they mention that examination of eye scrapings for vitamin-A deficiency gave positive results. In a report of a typical case, a 2-year-old girl, they state that examination of the eyes revealed blue scleras and very pale and dry conjunctivas, and that the child cried without tears.

The cases of Van der Sar (1951) in Curaçao had xerophthalmia, one of which is illustrated, and the case pictured in Fig. 5 of his paper appears to the present writer to have xerosis conjunctivae. Blepharitis and other mucocutaneous lesions were frequent.

Finally, from British Guiana, Herlinger (1950) mentions that signs of vitamin-A deficiency do not occur there in children with kwashiorkor.

### *North America and Europe*

In conclusion, considering these two areas together, one finds the same close association of vitamin-A deficiency and protein malnutrition in the early accounts of the syndrome from places where it no longer occurs, and in at least one present-day description.

Czerny & Keller (1928) in their classical monograph on *Mehlnährschaden*, or carbohydrate dystrophy, make mention of xerophthalmia as a feature of some of their cases, and other accounts from Germany include those of Stolte (1922), and of Finkelstein (1921), who recognized that fully developed

*Mehlnährschaden* might include in its symptomatology, in addition to oedema, keratomalacia and spasmophilia.

In adults suffering from famine oedema in Europe during and just after the First World War, the signs of milder vitamin-A deficiency, such as night blindness and xerosis conjunctivae, were noted in Germany (Schittenhelm & Schlecht, quoted by Jackson, 1925) and in Poland (Budzynski & Chelckowski, 1916) and were also mentioned by Maver (1920) in an extensive review of famine oedema.

The well-known accounts by Bloch (1921, 1924a, 1924b) of the widespread outbreak of vitamin-A deficiency in Denmark during this period laid stress on the general dystrophic signs, and some of his pictures closely resemble those of present-day kwashiorkor. Also in Denmark, Blegvad (1924), in a review of the early literature on xerophthalmia, mentioned that seven authors had described keratomalacia in association with *Mehlnährschaden*, and amongst his series of 453 cases of keratomalacia, he found that in 20 fatal cases which were autopsied, 3 had "hepatic fatty degeneration" and 2 "hepatic steatosis".

There is a number of early accounts of *Mehlnährschaden* from the USA, but the only one the writer has found which includes keratomalacia in the symptomatology is that of Ross (1921), who described four such cases in Baltimore, Md.

Protein malnutrition still exists in some parts of southern and eastern Europe, but the only account (Frontali, 1948) known to the writer which includes keratomalacia comes from the southern part of Italy, where it appears to occur quite commonly.

### Etiology

It should be evident from this review that serious eye lesions may be one of the most frequent and important complications of the protein malnutrition syndrome. The question naturally arises as to how these changes are brought about. Those of a less serious nature, and probably due to deficiency of B-complex vitamins, such as angular blepharitis, circumcorneal injection, and photophobia, will not be considered here. Attention will be concentrated upon the blinding conditions xerophthalmia and keratomalacia, attributable only, so far as we know at present, to deficiency of vitamin A.

Theoretically, protein lack may adversely affect the following stages of the metabolism of vitamin A:

1. *Absorption.* The concentrations of pancreatic and intestinal enzymes are known to fall and histological changes occur in these structures in protein malnutrition, both human and animal.

2. *Conversion of carotene to vitamin A.* This is known to occur chiefly in the small intestine and may be impaired in protein malnutrition.



3. *Transport.* Except for vitamin A newly absorbed from the intestine, most of the vitamin is present in the blood as the free alcohol, loosely attached to protein which is thought to be albumin.

4. *Storage.* This occurs mainly in the liver, and there chiefly in the reticulo-endothelial cells. It is not known whether fatty infiltration of parenchymatous liver cells would seriously impair this storage.

5. *Utilization at the cellular level.* Outside the retina, almost nothing is known about the function of vitamin A in cellular metabolism. Recent electron-microscope studies (Sheldon & Zetterqvist, 1956) indicate that the mitochondria are seriously deranged in vitamin-A deficiency, and disordered protein metabolism would certainly have some additional adverse effect on these vital cellular structures.

At present there is no real evidence that any of these possibilities does in actual fact operate in the development of vitamin-A deficiency as a complication of protein malnutrition. Most important from the practical point of view, and relatively easy to ascertain, is the actual daily intake of the vitamin in the breast milk and other dietary constituents of malnourished children. The writer feels confident that, when this is done, a low intake of vitamin A will be shown to be by far the most frequent cause of eye signs in protein malnutrition.

### Conclusions

Consideration of the numerous accounts from most parts of the world of the close association of eye signs with protein malnutrition makes it imperative, in view of the serious consequences of impairment or loss of vision, that in such cases

- (a) the eyes be always fully examined;
- (b) their condition be carefully noted in reports of protein malnutrition; and
- (c) the significance, to the writers of such reports, of the terms they use be clearly explained.

With regard to therapeutic and prophylactic measures, it seems probable from the work which has been done that, even in the absence of gross physical signs, the vitamin-A stores are low in the protein-malnourished child. Consequently, correction of this should be part of any programme of treatment.

### RÉSUMÉ

Le syndrome de carence protéique connu sous des noms divers, tels que kwashiorkor, stéatose du foie, dystrophie nutritionnelle, est largement répandu dans la plupart des collectivités sous-alimentées. Le tableau clinique varie considérablement d'une région à l'autre. C'est ainsi que certains rapports font état de lésions oculaires, ou signalent leur

absence, alors que d'autres sont muets sur ce point. Il s'agit pourtant d'une complication importante qui conduit souvent à la cécité. Elle n'a pas reçu jusqu'ici l'attention qu'elle mérite.

L'auteur passe en revue les descriptions du syndrome, anciennes et récentes, et cite de nombreux cas où les lésions oculaires étaient associées à l'insuffisance protéique. De ce panorama général de la littérature qui porte sur toutes les parties du monde, il ressort que les complications oculaires sont dues à une déficience vitaminique concomitante (avitaminose A dans les lésions qui, comme la xérophtalmie, aboutissent à la cécité, et avitaminose B dans les atteintes moins graves) plutôt qu'à la carence protéique elle-même, comme l'avaient pensé certains auteurs.

Théoriquement, la carence en protéines peut entraver de plusieurs façons le métabolisme de la vitamine A. Elle peut gêner l'absorption, l'accumulation ou le transport de la vitamine dans l'organisme ou la transformation du carotène en vitamine A. Il se peut aussi qu'une perturbation du métabolisme des protéines inhibe d'une manière ou d'une autre le métabolisme de la vitamine A dans le métabolisme cellulaire — action très mal connue sauf en ce qui concerne la rétine — mais la portée pratique de ces recherches demande encore à être précisée. Selon l'auteur, c'est probablement la pauvreté du régime en vitamine A qui est la cause principale des lésions oculaires. C'est donc à remédier à cette carence que doivent s'attacher essentiellement les efforts de prévention des lésions oculaires. Il semble, d'après les travaux accomplis, que même en l'absence de signes physiques patents, les réserves de vitamine A sont faibles chez les enfants carencés en protéines. Aucun programme de traitement ne devrait donc négliger ce point.

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